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> ONE MONTH, ONE PROTEIN <

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rupture

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Who has not been accosted by someone they would prefer to avoid? You greet them meekly, exchange a few polite words while wondering how to cut the exchange short without being disrespectful. If being disrespectful is not an issue, however, things become gloriously easy. You could tell them that their company bores you, that you have more important things to tend to or interrupt the chat with a brisk shake of the hand and move on. If you were part of a cartoon strip, you could burst into flames or simply disintegrate. It so happens that cells can actually opt to disintegrate when dealing with something that has become toxic to their environment, or at any rate redundant. This can be a virus, a bacterium, or perhaps simply age. Such an option is generally called programmed cell death, or apoptosis. And as there are many ways of being disrespectful to your acquaintance, there are many ways a cell can choose to disappear. One is by generating fatal rips in its own plasma membrane. Though rips such as these have been observed by scientists for many years, plasma membrane rupture was long believed to be a passive event. Until a protein known as ninjurin-1 was discovered.

Manawatu Gorge

by Timon Maxey, New Zealand
instagram: @timonmaxey

courtesy of the artist

Though a subtle difference between programmed cell death (PCD) and apoptosis is under debate, today, both words are usually used to describe the same thing by the great majority of biologists. That is to say, the intrinsic 'choice' a cell makes to end its own life. This is opposed to 'necrosis', the term used when a cell dies due to external factors, such as a cardiac arrest or poisoning. The word 'apoptosis' has Greek roots and literally relates to the periodic shedding of leaves in autumn. Hippocrates used it to describe gangrene, perhaps because he saw it as a kind of shedding of the skin. Almost two thousand years later, during the 18th and the 19th centuries, scientists began to take an interest in cell death which, in those days, was referred to as 'natural cell death'.

Until the early 20th century, the causes of natural cell death were attributed to mechanical changes, such as the swelling and subsequent bursting of a cell. However, the Scottish microbiologist Alexander Fleming (1881-1955) suggested that cell death could also be caused by chemical changes, such as the disintegration of the cell's chromatin which he had observed under the microscope. The term 'programmed cell death' only appeared in the early 1960s. From a purely philosophical point of view, the notion that a cell could choose to die – albeit under given circumstances – seemed almost unethical. However, the 1970s and the advent of molecular biology changed such views which, all of a sudden, became attractive: a cell could plan its own demise.

A cell can choose to put an end to its life in several ways. Frequently, more than one strategy is used: two strategies can occur in unison for instance, or one can trigger off a second. Sometimes, too, a cell can decide to delay its death to arrange a few things beforehand – this has been described in a previous article*. Which

strategies does a cell choose? It can form pores in its plasma membrane, for example, fragment its DNA, or slow down its mitochondria. Each of these strategies is fatal, by letting vital constituents leave the cell, inhibiting novel protein synthesis or failing to provide ATP, respectively. If performed simultaneously, little hope is left for the cell. The upside? No harm is caused to neighbouring cells – as opposed to necrosis.

Rips, or tears, on a cell's plasma membrane had been observed for centuries and scientists thought they were passive, purely due to mechanical forces – following the swelling of a cell for instance, much like stretch marks that appear on skin when weight has been put on abruptly. However, it turns out that rips, or plasma membrane ruptures, are quite intentional. This became obvious when researchers discovered the protein ninjurin-1. Ninjurin-1 is widely expressed, especially in tissues of epithelial origin, where it seems to be involved in cell adhesion. Structurally, ninjurin-1 looks like a hairpin. The curved bend is formed by a pair of alpha-helices, as in a classic transmembrane protein embedded in the cellular membrane. The N- and C-terminal extremities jut out to bathe in the extracellular medium, and the N terminus carries 2 alpha-helices (alpha1 and alpha2) separated by a kink.

Scattered across a cell's plasma membrane, monomeric ninjurin-1 is inactive. But during PCD, researchers noticed that ninjurin-1 monomers polymerise to form filaments of varied length. Structurally, each filament is built in the style of a classical wooden fence. The transmembrane region remains embedded in the cellular membrane while the N-terminus plunges into it. Alpha2 positions itself parallel to the sides of the hairpin while, thanks to the kink, alpha1 juts out at 90 degrees, reaching out to bind to a neighbouring monomer. The height of each filament, or 'ninjurin-fence', thus spans the width of the cellular membrane. In this way, filaments form linear tears in the membrane, or their ends meet to form pore-like structures. Either way, vital cytosolic constituents are free to spill out into the extracellular medium.

PCD was observed in multicellular organisms to begin with. In fact, for a long time, it was thought that the notion of PCD could only apply to multicellular organisms, or at least to cells where some kind of cooperation, or sort of cellular society, exists. But towards the end of the 20th century, it became apparent that PCD also applied to unicellular organisms. In fact, researchers now believe that PCD actually originated in unicellular organisms – although, admittedly, the existing theories do point, one way or another, towards multicellular cooperation. As an example, in a colony of bacteria, an infected cell could decide to give up its life to put a halt to viral replication and, hence, the further spread of infection.

How is ninjurin-1 activated? Is it the target of another factor triggered off by PCD? Does it react to a molecular change in the plasma membrane? Or to a conformational change such as membrane swelling? Ninjurin-1 may respond to both kinds of cue – chemical and mechanical. So far, no one knows. Some helices, such as those found in ninjurin-1, are known to sense lipid-packing defects or inflections of the membrane, both of which could be the result of cell swelling. Despite its seemingly tragic outcome, PCD is an elegant biophysical mechanism used by cells to create fatal tears in their own membrane without causing damage to their neighbours. In fact, frequently, it is precisely to preserve them from harm. A mechanism such as this could open opportunities for healing cancers, infection and inflammatory diseases by forcing cells that have become harmful to their environment to commit suicide.

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Cross-references to UniProt

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